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[redacted] CONFERENCE ON SEARCH FOR ANTIBACTERIAL, ANTIVIRUS, AND ANTICANCER ANTIBIOTICS

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An interinstitutional conference, organized by the Institute of Search for New Antibiotics of the Academy of Medical Sciences USSR and devoted to the discussion of methods of searching for antibacterial, antivirus, and anticancer antibiotics, was held 16-17 May 1955.

Besides the members of the staff of the above-mentioned institute, workers from the Institute of Virology imeni D. I. Ivanovskiy, the Institute of Experimental Pathology and Therapy of Cancer, the Institute of Epidemiology and Microbiology imeni N. F. Gamaleya of the Academy of Medical Sciences USSR, the All-Union Scientific Research Institute of Antibiotics of the Ministry of Health USSR, the Institute of Microbiology of the Academy of Sciences USSR, and the Laboratory of Antibiotics at Moscow State University imeni M. V. Lomonosov participated in the conference.

S. D. Yudintsev, director of the Institute of Search for New Antibiotics of the Academy of Medical Sciences USSR, in his introductory address indicated that the available antibiotics are being successfully utilized in the treatment of many infectious diseases. To this day, however, there are as yet no new antibiotics actually effective against virus infections and especially against malignant tumors. S. D. Yudintsev pointed to the overdue necessity for the discussion of questions connected with the development of methods for testing and for the selection of new antibiotics on the basis of their antibacterial activity and especially their antivirus and anticancer properties. Experimental material which permits some summation of the results of the work done and an exchange of experience gained has been accumulated at the Institute of Search for New Antibiotics, at the Institute of Virology, at the Institute of Experimental Pathology and Therapy of Cancer, and at the All-Union Scientific Research Institute of Antibiotics. The conference must make its contribution to the furthering of working contacts between the research institutions engaged in the search for new antibiotics.

A report by Prof G. F. Gause (Institute of Search for New Antibiotics, Academy of Medical Sciences USSR) on "Problems of the Classification of Actinomycete-Antagonists in Connection with the Search for New Antibiotics," was the first to be heard at the conference. At present, actinomycetes have acquired considerable importance as producers of antibiotic substances which inhibit the propagation of bacteria, rickettsiae, and some of the large viruses. Antibiotics which inhibit the growth of malignant tumors and render inactive small viruses, e.g., the influenza virus, have also been discovered in actinomycetes.

Classification and identification of actinomycete-antagonists have become of great importance in connection with the work of searching for new antibiotics. In the overwhelming majority of cases, different antibiotics are formed by different species of actinomycetes. The rapid solution of the question in regard to the species will make it possible to avoid unnecessary waste of time and labor in work on producers already described in the literature. Manuals for identification published to date cannot satisfy investigators who are working at the present level of the development of science, for many of the producers isolated from the soil appear to be new species. At the same time it must be noted that frequently at many laboratories cultures of actinomycetes which are

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of no interest as regards their relation to antibiotics are being discarded, so that a large number of new species of actinomycetes remain undescribed. This, undoubtedly, is also taking place at a number of laboratories abroad, where research work is being done on orders from commercial firms which pursue narrow utilitarian objectives.

In the course of a number of years the research personnel at the Laboratory of Antibiotics of the Academy of Medical Sciences USSR (Institute of Search for New Antibiotics of the Academy of Medical Sciences USSR) has subjected to study approximately 100,000 cultures of actinomycete-antagonists. This work bears witness to the unilateral character of the principles of classification which form the basis of the available manuals for the determination of actinomycetes. The author of the report pointed out that morphological, cultural, biochemical, serological, and other indicators must serve as the basis of classification. It is recommended that cultural and morphological characteristics be studied in connection with the cultivation of actinomycetes on definite media (the composition of the media was given). Of great importance, as one of the diagnostic indicators, is the color of the aerial (above surface) and substrate mycelium. The speaker thinks it expedient to group all closely related species into series on the basis of the coloration of the aerial and substrate mycelium. This will facilitate the work of determining and identifying according to species derivation the antibiotics newly isolated from the soil. There are 11 such series, and their number will probably grow in the future.

M. K. Solovyeva, Candidate of Medical Sciences, (All-Union Scientific-Research Institute of Antibiotics, Ministry of Health USSR) acquainted the conference with a plan for the study of antagonists, and with the basic stages for obtaining new antibiotics: first stage -- the separation of the cultures of microorganisms and the isolation of antagonists; second stage -- a broader study of the biological characteristics and evaluation of the antagonistic properties of the producers of antibiotics; third stage -- the selection of fermentation media for promising cultures; fourth stage -- the development of methods for the separation of the preparation from the culture liquid; and the final, fifth stage -- evaluation of the pharmacological, chemotherapeutic, and other properties of the preparation.

In connection with the fact that a very early evaluation of cultures of producers is one of the most important conditions of an effective search for new antibiotics, an evaluation and selection of cultures on the basis of their action on saprophytic and pathogenic microorganisms, as well as on the basis of their antivirus and antitumor activity (an evaluation of the activity of the latter type is in progress at the Institute of Experimental Pathology and Therapy of Cancer) is already carried out in the second stage -- the stage of the culture liquid. Under such an arrangement of the work it is possible to reject, at a comparatively early stage, about 90-95 percent of the cultures, and to concentrate attention on strains which are promising.

Solovyeva pointed out the importance of utilizing as test bacteria in the search for new antibiotics those belonging to strains which have been adapted to penicillin, streptomycin, and other antibiotics widely used at the present time. According to the data furnished by her, some of the generally accepted tests are not always adequate as a basis for judging the action of antibiotics on different groups of microorganisms.

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M. G. Brazhnikova, Doctor of Biological Sciences, devoted her report to questions of the early identification of antibiotics of actinomycete origin on the basis of their chemical characteristics. She thinks that although definite antibiotics which belong to various classes of chemical compounds are derived from some definite species of actinomycetes, there are, nevertheless, many exceptions to the rule. A number of facts indicate that the discovery of a new species of an actinomycete-antagonist is not necessarily followed by the discovery of a new antibiotic. Therefore, alongside the classification of actinomycetes, there must be developed a classification of antibiotics on the basis of their chemical, physical, and biological properties.

Despite many attempts, it is not as yet possible to identify antibiotics in the stage of the culture liquid. In most cases it is already possible to determine at the stage of the semipurified preparation whether a given antibiotic belongs to any one of the well-known groups or whether it is a new one.

In the opinion of the speaker, it is necessary at present to compile a complete record of the characteristics of all known groups of antibiotics on the basis of the following indexes: the method of isolation from the culture liquid; extraction by solvents at various pH values; solubility in a number of organic solvents and water; activity per milligram of weight; behavior towards ion-exchange resins; capacity to form some difficult soluble crystalline salts; chromatographic properties; stability towards alkalis and acids; ultraviolet absorption spectra; qualitative reactions; spectrum of antibacterial activity; toxicity; therapeutic action in experiments on animals.

Simultaneously with the search for new antibiotics suitable for clinical use, systematic and thorough work on establishing the characteristics of antibiotics which represent new classes of chemical compounds is necessary. The efforts and means which will be spent on the isolation and study of such antibiotics will be fully compensated by the wealth of new material that will aid in the rational systematization of antibiotics, and by the fact that duplication in the work of isolating new antibiotics will be avoided.

A paper by Docent N. S. Yegorov (Laboratory of Antibiotics, Moscow State University imeni M. V. Lomonosov) was devoted to conditions under which antagonism manifests itself in actinomycetes. A thorough study of the strains which initially seem only slightly active is necessary, since antibiotics isolated from highly productive as well as slightly productive cultures may be of therapeutic value. There is now a sufficient number of methods for increasing the yield of antibiotics. The antibiotic properties of a certain actinomycete may be manifested in some media, and not manifested in others. In this connection a number of media must be developed which will contribute to the maximum antibiotic activity of actinomycete-antagonists.

T. I. Preobrazhenskaya, Candidate of Biological Sciences, (Institute of Search for New Antibiotics, Academy of Medical Sciences USSR) reported on work [illegible] with the classification and characterization of actinomycete-antagonists of the Lavendulae-roseus series.

M. N. Slinkina, Candidate of Biological Sciences, (Institute of Search for New Antibiotics, Academy of Medical Sciences USSR) in her report dwelt on the isolation and early identification of antibiotics belonging to the group of actinomycetes.

The second day of the conference opened with a report by V. A. Zhorin Director of Medical Sciences, (Institute of Search for New Antibiotics Academy of Medical Sciences USSR) on "Methods of Searching for New Antibiotics Possessing Antivirus Activity." The use of bacteriophages as a test object in the selection of antibiotics, in the speaker's opinion, is little justified, because in a large number of cases there is no parallelism between the action of antibiotics on bacteriophages on the one hand, and their action on human and animal viruses, on the other hand. The use of the virus of tobacco mosaic is suggested for the primary selection of antivirus antibiotics. After the cultivation of the actinomycete on an agarized medium, blocks were cut out and placed upon the upper surface of leaves of thorn apple or tobacco, about 20-30 minutes before that infected with the virus of tobacco mosaic. The action of the antibiotic produced by the actinomycete was estimated on the basis of the number of point necroses under the blocks and on the free surface of the leaf. Another variant of this method is the mixing of the cultural liquid with a suspension of the virus of tobacco mosaic, placing it upon the surface of the leaves, and recording the number of point necroses.

Another method of selection used at the Institute of Search for New Antibiotics, Academy of Medical Sciences USSR, is that of testing the action of culture liquids as well as of preparations of antibiotics upon the influenza virus. In carrying out these tests, a suspension of ground lungs of mice infected with influenza virus was mixed with the culture liquid or with a solution of the antibiotic, after which new animals were infected.

On the basis of the work done at the institute, the author of the report arrived at the conclusion that actinomycetes which yield substances neutralizing the virus of influenza and the virus of tobacco mosaic occur widely in nature. The rate of coincidence in the viricidal action of the culture liquid as tested on the virus of tobacco mosaic used as a model and its action on the influenza virus reached the figure of 9%. A number of antibiotics selected by this method was found to a more or less pronounced chemotherapeutic action in mice infected with the influenza virus. Work in this direction is being continued.

Prof V. D. Ryabkov (Moscow), Corresponding Member of the Academy of Sciences USSR, in his report on "Types of Compounds Which Inhibit Propagation of Viruses," dwelt in detail on the question of applying the results obtained in work on model viruses to human virus diseases. The speaker thinks that it is not possible to foretell whether an inhibitor will be therapeutically beneficial on the basis of the fact that it suppresses a virus in vitro. Experiments must be made on animal viruses in experimental virus infections, and models must be selected on the basis of the phylogenetic principle, one model representing three or four closely related viruses. It must be taken into consideration that a virus in vitro is in a "quiescent form," and is more resistant to various types of action exerted on it than the virus which is in definite stages of its cycle of development in the organism.

The author of the report arranged the compounds which inhibit the propagation of viruses into groups on the basis of their action on specific aspects of metabolism, and noted that there are few ideal selectively acting inhibitors. An inhibitor, while suppressing related processes of metabolism both in the host and the virus, may still be capable of therapeutic action, if the suppression of these processes proceeds at unequal rates.

In conclusion the report stressed the great variability of the results of experiments with viruses, and the necessity for a statistical evaluation of the data obtained.

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M. A. Zaytsenok, Candidate of Medical Sciences, (Institute of Virology imeni D. I. Ivanovskiy) reported on methods of investigating the inhibiting action exerted by various substances on the influenza and vaccinia viruses.

In studying the action of various substances on the propagation of the influenza virus in chicken embryos, the following data may serve as indicators of the degree of virus accumulation: (a) the percentage of embryos with a positive hemagglutination reaction (HRA), (b) the percentage of embryos with a relatively high HRA titer; and (c) the coefficient of inhibition, which represents the ratio of the mean geometric titers found in experiments to those found in control tests competed in relation to embryos with a positive HRA.

A comparative titration of the vaccinia virus under dynamic conditions in a suspension of chorio-allantoic membranes of infected chicken embryos has shown the complete correspondence between changes in the HRA titer and changes in the titer of infectiousness, as determined by the infection of chicken embryos, rabbits, and guinea pigs. In studying the effect of various preparations on the multiplication of the vaccinia virus in the chorio-allantoic membrane of chicken embryos, it is possible to evaluate the inhibiting action exerted on the virus on the basis of the reduction in the percentage of embryos with a positive HRA, as well as by taking into consideration the number of embryos in which visible foci of afflicted membrane have developed.

When susceptible tissues have been infected with a mixture of the virus with certain substances, a delay in the development of the virus is observed. In this connection, the effect produced by different substances is exerted by different means. Some inhibitors, upon contact with the virus in vitro, lower the latter's titer of infectiousness; that is, they have a virucidal activity. Others produce no virucidal effect upon contact with the virus in vitro, but possess virustatic activity, which is exerted through the cells and tissues of the host.

Considerable interest was aroused by a report given by Prof M. M. Mayevskiy, Corresponding Member of the Academy of Medical Sciences USSR, (Institute of Experimental Pathology and Cancer Therapy) and entitled "Problems of Searching for Antibiotics Possessing Anticancer Activity." The author of the report pointed out that the prospects of finding antibiotics active against cancer are very small. The main difficulties encountered in this work are (1) lack of an exact knowledge of the etiology of tumors, and (2) the impossibility in a number of cases of transferring to the clinic results obtained on experimental tumors. Nevertheless, it is better that antibiotics be selected on the basis of tests carried out on experimental tumors, because tests of other types suggested in recent years, for instance, the Albecker yeast test, have proven to be of little value.

The study of the action of antibiotics on the cells of malignant neoplasms may be conducted in several ways. The cells may be treated with the inhibitors under examination and observed under a microscope. The results obtained are not always confirmed in vivo, however. It is more expedient to test the inoculation effectiveness of the material treated with the inhibitor, and to calculate the percentage of inoculations which have a lasting effect. The embryo method is very convenient. Finally, the most reliable method is that of carrying out tests on animals which have been infected with a specific type of tumor.

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Mayevskiy dwelt on the number of animals which have to be used to obtain reliable results and the time of observation which is necessary, emphasizing that the difference between the test and the control emerges with greater sharpness after a long observation. It is expedient to evaluate the results on the basis of the area of the tumor while the test is in progress, and on the basis of the weight of the tumor at the end of the test, after the animals have been killed. It has been noted that preparations may be injected at considerable intervals of time.

In conclusion Mayevskiy emphasized the necessity for a thorough study of the differences between induced and spontaneous malignant neoplasms, stressing that the selection of antibiotics must be done on induced tumors, which to a considerable degree lowers the value of the method.

On the same day the participants at the conference heard the following reports listed in the program: O. K. Kosolimo (Institute of Search for New Antibiotics, Academy of Medical Sciences USSR), "Study of Antitumor Activity of Some New Antibiotics"; N. S. Dreyzin (Institute of Virology imeni D. I. Ivanovskiy), "Materials Pertaining to the Study of the Effect of Antibiotic Preparations on the Influenza Infection"; and M. S. Ruchkina, "The Distribution Within Various Systematic Groups of Actinomycete-Antagonists Possessing Antivirus Activity."

In evaluating the work and the results of the conference, note must be taken, first of all, of the matter-of-fact manner in which the problems were set. The conference was conducted in a methodical manner, and principal attention was given to the description of methods of work, with factual material being used to illustrate the premises made.

The most animated discussion was aroused by problems pertaining to the selection of antivirus and anticancer antibiotics with the use of different models and also by questions connected with principles of the rational classification of actinomycete-antagonists that would facilitate practical work. A number of the best-suited models for various stages of work in the selection of antibiotics was pointed out, and an evaluation of the morphological and physiological properties of the producers of antibiotics as indexes for classification was given.

Prof S. F. Gause, in his concluding remarks, pointed out that in the critical discussion and selection of the most promising methods of work it is not necessary to strive for absolute identity of methods applied at all research institutions.

The first conference held by the Institute of Search for New Antibiotics of the Academy of Medical Sciences USSR was devoted to very essential problems, and is of significance as the beginning of a systematic exchange of opinions between investigators engaged in the search for new antibiotics.

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